04-C-0080: Phase II Trial of Pirfenidone in children, Adolescents, and Young Adults with Neurofibromatosis Type 1 and Progressive Plexiform Neurofibromas

Neurofibromatosis Type 1 (NF1) is an autosomal dominant, progressive genetic disorder characterized by diverse clinical manifestations. Patients with NF1 have an increased risk of developing tumors of the central and peripheral nervous system including plexiform neurofibromas, which are benign nerve sheath tumors that may cause severe morbidity and possible mortality. The histopathology of these tumors suggests that events connected with formation of fibroblasts might constitute a point of molecular vulnerability. Gene profile analysis demonstrates overexpression of fibroblast growth factor, epidermal growth factor, and platelet-derived growth factor in plexiform neurofibromas in patients with NF1. Pirfenidone is a novel anti-fibrotic agent that inhibits these and other growth factors. Clinical experience in adults has demonstrated that pirfenidone is effective in a variety of fibrosing conditions and pirfenidone is presently under study in a phase II trial for adults with progressive plexiform neurofibromas. A phase I trial of pirfenidone in children and young adults with NF1 and plexiform neurofibromas is nearing completion, and has established the phase II dose (the dose resulting in a mean drug exposure [AUC] not more than 1 standard deviation below the mean drug exposure [AUC] in adults who received pirfenidone at the dose level demonstrating activity in fibrosing conditions). Pirfenidone has been well tolerated, and no dose-limiting toxicities have been observed. The phase II dose will be used in a single stage, single arm phase II trial of pirfenidone in children and young adults with NF1, who have progressive plexiform neurofibroma(s) to determine whether this drug increases the time to disease progression. The natural history of the growth of plexiform neurofibromas is unknown. For this reason, time to disease progression on the placebo arm of an ongoing NCI POB placebo-controlled, double-blind, cross-over phase II trial of the farnesyltransferase inhibitor R115777 for children and young adults with NF1 and progressive plexiform neurofibromas will be used as historical control to determine if pirfenidone increases time to disease progression. Eligibility criteria and method of tumor measurements are identical for both trials. Pirfenidone will be administered orally as capsules at a dose of 500 mg/m^2 three times a day (q8h) for cycles of 28 days with no rest period between cycles based on the results of our pediatric phase I trial.

ELIGIBILITY CRITERIA

Inclusion Criteria

Age: ≥3 years and ≤21 years of age. Required body surface area (BSA): ≥ 0.31 m^2.

Diagnosis: Patients with NF1 and progressive plexiform neurofibromas that have the potential to cause significant morbidity, such as (but not limited to) head and neck lesions that could compromise the airway or great vessels, brachial or lumbar plexus lesions that could cause nerve compression and loss of function, lesions that could result in major deformity (e.g., orbital lesions) or significant cosmetic problems, lesions of the extremity that cause limb hypertrophy or loss of function, and painful lesions. Histologic confirmation of tumor is not necessary in the presence of consistent clinical and radiographic findings, but should be considered if malignant degeneration of a plexiform

neurofibroma is clinically suspected. In addition to plexiform neurofibroma(s), all study subjects must have at least one other diagnostic criteria for NF1 listed below (NIH Consensus Conference):

- Six or more café-au-lait spots (≥0.5 cm in prepubertal subjects or ≥1.5 cm in postpubertal subjects)
- Freckling in the axilla or groin
- Optic glioma
- Two or more Lisch nodules
- A distinctive bony lesion (dysplasia of the sphenoid bone or dysplasia or thinning of long bone cortex)
- A first-degree relative with NF1

In this study a plexiform neurofibroma is defined as a neurofibroma that has grown along the length of a nerve and may involve multiple fascicles and branches. A spinal plexiform neurofibroma involves two or more levels with connection between the levels or extending laterally along the nerve.

Measurable Disease: Patients must have measurable plexiform neurofibroma(s). For the purpose of this study a measurable lesion will be defined as a lesion of at least 3 cm measured in one dimension. There must be evidence of recurrent or progressive disease as documented by an increase in size or the presence of new plexiform neurofibromas on MRI. Progression at the time of study entry is defined as:

- A measurable increase of the plexiform neurofibroma (≥ 20% increase in the volume, or a ≥ 13% increase in the product of the two longest perpendicular diameters, or a ≥ 6% increase in the longest diameter) over the last two consecutive scans (MRI or CT), or over the time period of approximately one year prior to evaluation for this study.
- Patients who underwent surgery for a progressive plexiform neurofibroma will be eligible to enter the study after the surgery, provided the plexiform neurofibroma was incompletely resected and is measurable.

Prior therapy:

- Patients with NFI are eligible at the time of recurrence or progression of an inoperable plexiform neurofibroma.
- Patients will only be eligible if complete tumor resection is not feasible, or if a patient with a surgical option refuses surgery.
- Since there is no standard effective chemotherapy for patients with NF1 and progressive plexiform neurofibromas, patients may be treated on this trial without having received prior medical therapy.
- Patients must have recovered from the toxic effects of all prior therapy before entering this study. The Cancer Therapy Evaluation Program Common Terminology Criteria (CTCAE-3) Version 3.0 will be used for toxicity assessment. A copy of the CTCAE version 3.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). Recovery is defined as a toxicity grade <2, unless otherwise specified in the Inclusion and Exclusion Criteria.
- Patients must have had their last dose of radiation therapy at least six weeks prior to study entry, and their last dose of chemotherapy at least four weeks prior to study entry. Patients who received G-CSF after the prior cycle of chemotherapy must be off G-CSF for at least one week prior to entering this study.

Performance Status: Patients should have a life expectancy of at least 12 months. Patients > 10 years must have a Karnofsky performance level ≥ 50, and children ≤ 10 years must have a Lansky performance level ≥ 50. (See Appendix 2). Patients who are wheelchair bound because of paralysis should be considered "ambulatory" when they are up in their wheel chair.

Hematologic Function: Patients must have an absolute granulocyte count ≥1,500/μL, a hemoglobin ≥ 9.0 gm/dl, and a platelet count ≥150,000/μL at study entry (all transfusion independent).

Hepatic Function: Patients must have a bilirubin within normal limits and SGPT ≤ 2x upper limit of normal. Patients with Gilbert syndrome are excluded from the requirement of a normal bilirubin. (Gilbert syndrome is found in 3-10% of the general population, and is characterized by mild, chronic unconjugated hyperbilirubinemia in the absence of liver disease or overt hemolysis).

RENAL FUNCTION: Patients must have an age-adjusted normal serum creatinine (see table below) OR a creatinine clearance ≥ 70 mL/min/1.73 m^2.

AGE (YEARS)	MAXIMUM SERUM CREATININE (MG/DL)
≤ 5	0.8
5 < AGE ≤ 10	1.0
10 < AGE ≤ 15	1.2
> 15	1.5

Informed Consent: All patients or their legal guardians (if the patients is <18 years old) must sign an IRB approved document of informed consent (screening protocol) prior to performing studies to determine patient eligibility. After confirmation of patient eligibility all patients or their legal guardians must sign the protocol specific informed consent to document their understanding of the investigational nature and the risks of this study before any protocol related studies are performed (other than the studies which were performed to determine patient eligibility). When appropriate, pediatric patients will be included in all discussions. Age appropriate assent forms for children from 7 through 12 years, and for children from 13 through 17 years have been developed and will be signed by the pediatric patients, when appropriate, in order to obtain written assent.

Durable Power of Attorney (DPA):

- All patients ≥18 years of age will be offered the opportunity to assign DPA so that another person can make decisions about their medical care if they become incapacitated or cognitively impaired.
- Patients must be able to take pirfenidone by mouth. Capsules can be opened and content mixed with food for easier consumption in small children.

- Patients (both male and female) must be willing to practice birth control (including abstinence) during and for two months after treatment, if of a child-bearing age. For purposes of the protocol, all patients greater than 9 years of age or those showing pubertal development will be considered of childbearing age.
- Ability to undergo MRI examinations following the MRI protocol outlined in Appendix 4.

EXCLUSION CRITERIA

- Pregnant or breast feeding females are excluded, because the toxic effects and pharmacology of pirfenidone in the fetus and newborn are unknown.
- Clinically significant unrelated systemic illness (serious infections or significant cardiac, pulmonary, hepatic or other organ dysfunction), which in the judgment of the Principal or Associate Investigator would compromise the patient's ability to tolerate pirfenidone or are likely to interfere with the study procedures or results.
- An investigational agent within the past 30 days.
- Ongoing radiation therapy, chemotherapy, hormonal therapy directed at the tumor, immunotherapy, or biologic therapy (for example interferon).
- Inability to return for follow-up visits or obtain follow-up studies required to assess toxicity and response to therapy.
- Prior treatment with pirfenidone.
- Evidence of an optic glioma, malignant glioma, malignant peripheral nerve sheath tumor, or other cancer requiring treatment with chemotherapy or radiation therapy.

Pre-Treatment Evaluation

- History and physical, Quality of Life Assessment
- Laboratory work including hematology and chemistries (within 2 weeks prior to enrollment), pregnancy test (within 72 hours),
- MRI all measureable disease sites within 2 wks of enrollment & volumetric (3D) MRI imaging of progressing plexiform neurofibroma
- Biopsy of plexiform neurofibroma, only if clinically indicated.

GENERAL TREATMENT PLAN:

Open label phase II trial of oral pirfenidone. Patients will receive pirfenidone orally as capsules three times a day ("approximately" q8hours) for cycles of 28 days with no rest period between cycles (28 day treatment cycles). The dose of pirfenidone will be 500 mg/m^2 q8 hours (1500 mg/m^2/day). Patients can expect to stay in the area for approximately 2 days for the initial work-up. Treatment is outpatient unless otherwise clinically indicated.

Accrual

The protocol will be open to patient accrual in July 2004 at the POB and participating institutions around the country.